Paraplegia **28** (1990) 441–447 0031–1758/90/0028–0441 $10.00

Paraplegia

Serum Alkaline Phosphatase and Inorganic Phosphorus Values in Spinal Cord Injury Patients with Heterotopic Ossification

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Summary

The blood chemistry was studied in 140 spinal cord injury (SCI) patients (acute injury ward), including 18 patients who developed heterotopic ossification (HO). Comparisons between the HO and non-HO groups were made to determine if the alkaline phosphatase (AP), inorganic phosphorus (P), or calcium (Ca) levels were of diagnostic value. The results showed that AP, P, and Ca by themselves were of little help in the diagnosis of HO. However, the combination of elevated AP and P was significant, especially if both were consistently elevated. There were no significant differences between the HO and non-HO groups concerning completeness or level of spinal injury.

Key words: *Spinal cord injury; Heterotopic ossification; Alkaline phosphatase; Inorganic phosphorus*

Although some research workers have pointed out that an increased alkaline phosphatase (AP) value is not necessarily associated with heterotopic ossification (HO) (Rossier *et al.*, 1973; Bergmann *et al.*, 1977; Orzel and Rudd, 1985; Stover, 1986), it has been suggested that an elevation of AP is the most reliable indicator of HO in spinal cord injury (SCI) patients.

Several studies have also examined serum calcium (Ca) and phosphorus (P) levels in SCI patients and found them to be increased during the first 3 months following SCI (Chantraine *et al.*, 1970, 1971; Kaplan *et al.*, 1978; Bergmann *et al.*, 1977). Rarely, a relationship between serum P levels and HO has been demonstrated (Rossier *et al.*, 1973).

This study investigates SCI patients with and without HO in terms of differences in serum levels of Ca, P, and AP. It also examines the temporal relationship between these levels and various forms of bony injury, including bone fracture and bone surgery. These data could permit timelier and more accurate diagnosis of HO, and in addition, could provide further insights into the evolution of this disease.

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Methods

The subjects were 140 hospitalised SCI patients in an acute injury ward. Eighteen were diagnosed by radiography or bone scan as having HO, whereas 122 showed no evidence of the presence of such a condition. There were 137 males and 3 females. The age range was 18 to 83 years with a mean of 37·9. There were 87 patients with a cervical injury (including 9 with HO: 10·3%), 39 with a thoracic injury (including 9 with HO: 23·1%), and 14 with a lumbar injury (none of which showed evicence of HO: 0·0%). Sixty six had complete injuries (including 10 with HO: 15·2%) and 74 had incomplete injuries (including 8 with HO: 10·8%). Those who were treated with disodium etidronate (EHDP) before obtaining blood samples were excluded from the study.

Serum AP was measured by the automated method of Bessy, Lawry and Brock (1983). Normal levels were considered to be between 30 and 115 mu per ml. Inorganic P was measured in a Technicon Auto Analyzer system. Normal levels are 2·5 to 4·5 mg per dl. Ca was measured by Gitelman's modification of the automated procedure of Kessles and Wolfman (1983). Normal levels are 8·5 to 10·5 mg per dl.

Chi-square analysis was used to analyse the data, which were best represented by percentages, and analysis of variance was used to determine differences between means. The evolution of HO was divided into four phases: phase 1, date of injury to 4 weeks post-injury; phase 2, 4 to 8 weeks post-injury; phase 3, 8 weeks to 3 months post-injury; and phase 4, more than 3 months post-injury.

Results

There was a significant difference between the percentage of patients with HO at the three levels of SCI injury ($\chi^2[2] = 6{\cdot}19$, $p = 0{\cdot}045$). Post hoc comparisons showed non-significant differences between the cervical (10·3%) and thoracic (23·1%) groups; a significant difference between the cervical and lumbar (0·0%) groups; and a significant difference between the thoracic and lumbar groups. There was a non-significant difference ($\chi^2[1] = 0{\cdot}59$, $p = 0{\cdot}443$) between the percentage of patients with HO having complete injuries (15·2%) and those with HO having incomplete injuries (10·8%).

Table I shows the percentages of HO and non-HO patients having at least one blood test showing abnormal levels of AP, Ca, or P.

Table II shows the percentage of HO patients showing various combinations of abnormal AP, Ca, and P levels. Chi-square analysis revealed non-significant differences between the HO and non-HO groups.

Table III shows the percentages of HO and non-HO patients with abnormal AP and/or P levels for the fracture/bone surgery and non-fracture/bone surgery groups. Chi-square analysis revealed that fracture/bone surgery raises both the AP and/or P levels above those without fracture/bone surgery. However, the effects of fracture/bone surgery on AP and P are the same for those with HO and without HO.

The relationship between phase of injury and level and completeness is shown in Table IV. There was no statistically significant relationship between any of these factors. The development of HO in our sample was distributed across phases

Table I Percentage of HO and non-HO patients having at least one blood test resulting in levels of AP, P, or Ca beyond normal limits

Test	Non-HO	HO
AP>115·0	63·9	44·4
AP <30·0	4·1	0·0
Ca >10·5	16·4	5·6
Ca <8·5	35·2	22·2
P >4·5	86·9	83·3
P <2·5	10·7	0·0

Table II Percentage of HO and non-HO patients with combinations of AP and P, AP and Ca, or AP, P, and Ca elevated

Electrolytes	Non-HO	HO
AP >115 and P >4·5	43·4	61·1
AP >115 and P <2·5	4·1	0·0
AP >115 and Ca >10·5	4·1	5·6
AP >115 and Ca <8·5	14·8	5·6
AP >115 and Ca >4·5 and P >4·5	2·5	0·0

Table III Relationship between fracture/bone surgery, HO and non-HO, elevated AP and/or P

	Fracture/bone surgery			
	Yes (n = 121)		No (n = 19)	
Condition	Non-HO	HO	Non-HO	HO
AP >115	57·4	44·4	0·0	0·0
P >4·5	80·3	61·1	0·0	0·0
AP >115 and P >4·5	40·2	44·4	0·0	0·0

Table IV Relationship between phase, level of injury, and complete or incomplete injury for those patients with HO

	Cervical		Thoracic		Lumbar	
Phase	Complete	Incomplete	Complete	Incomplete	Complete	Incomplete
1	5·6	5·6	5·6	5·6	0·0	0·0
2	0·0	16·7	16·7	5·6	0·0	0·0
3	5·6	11·1	16·7	0·0	0·0	0·0
4	5·6	0·0	0·0	0·0	0·0	0·0

as follows: phase 1, 4 patients (22%); phase 2, 7 patients (39%); phase 3, 6 patients (33%); and phase 4, 1 patient (6%). The difference in percentages was not statistically significant. It should be noted that HO was not found in any of our patients with lumbar lesions.

Figure 1 shows the relationship between the likelihood of the development of HO and the proportion of blood tests showing elevated AP levels (>115). This likelihood, as measured by the difference in percentages between the HO and non-

HO patients, increased greatly if half or more of the blood levels of AP were elevated.

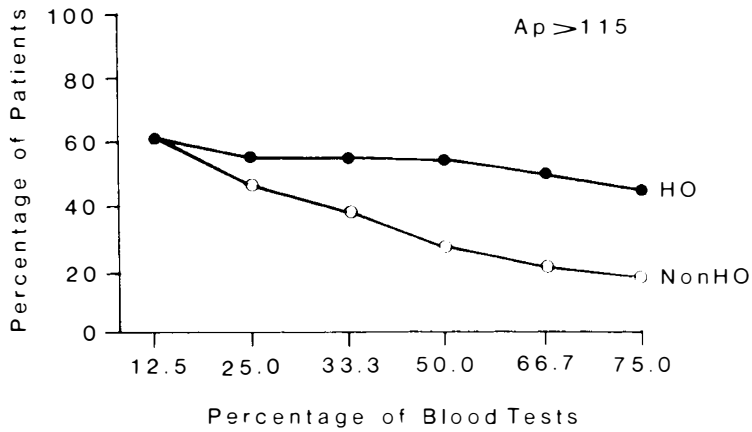

Figure 1 Percentage of HO and non-HO patients having AP >115 at 6 different percentages of blood tests.

Figure 2 shows the relationship between the likelihood of the development of HO and the proportion of blood tests showing elevated P levels (>4·5). There were no significant differences between the percentages of HO and non-HO patients at any of the percentages of blood tests. The likelihood of developing HO appeared to bear no relation to the proportion of blood tests showing elevated P levels.

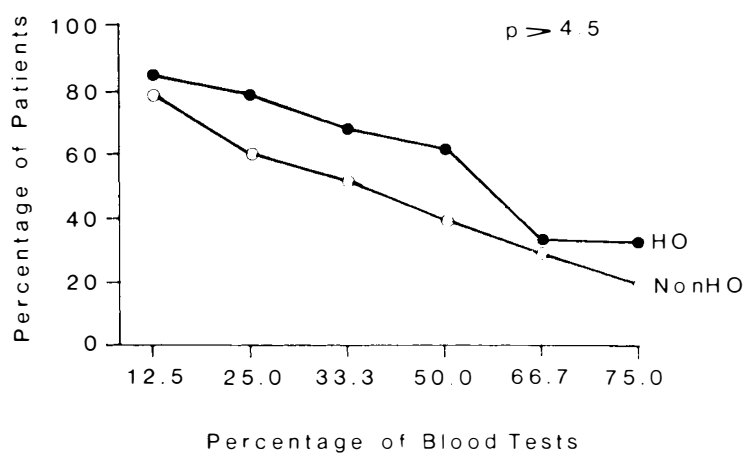

Figure 2 Percentage of HO and non-HO patients having P >4·5 at 6 different percentages of blood tests.

Figure 3 shows the relationship between the likelihood of developing HO and the proportion of blood tests showing elevation of both AP (>115) and P (>4·5). The difference between the percentage of HO and non-HO patients was significant at all percentages of blood tests. The likelihood of developing HO rose significantly as the proportion of tests showing elevation of both values increased.

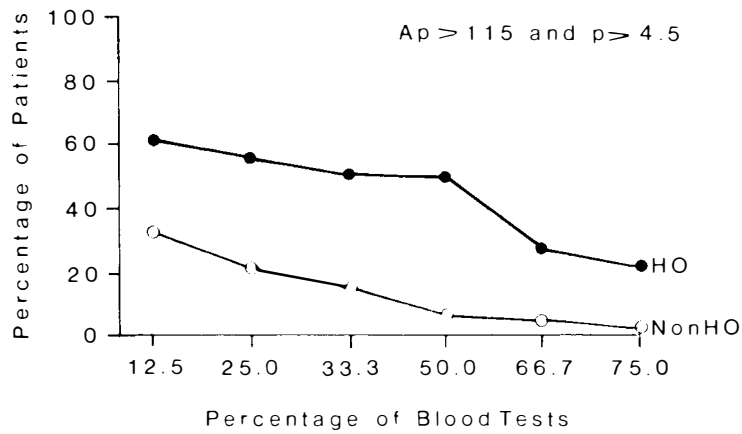

Figure 3 Percentage of HO and non-HO patients having AP >115 and P >4·5 at 6 different percentages of blood tests.

Discussion

The aetiology of HO remains unknown. Researchers have hypothesised various aetiologies, including biochemical factors (Farley and Baylink, 1982; Maugh, 1982), mesenchymal metaplasia (Ostrowski and Wlodarski, 1971), bone metabolism (Chantraine, 1971; Bergmann *et al.*, 1978), and trauma to joints (Silver, 1969; Kaplan *et al.*, 1978, Izumi, 1983).

It is well known that the major portion of serum AP originates from osteoblasts and chondroblasts. However, conflicting results have been obtained relative to serum AP levels in patients with HO (Kline, 1966; Nicholos, 1973; Orzel *et al.*, 1985; Bergmann *et al.*, 1977). This may be due in part to the presence of additional variables, especially the presence or absence of a fracture or bone surgery. At times consistent elevation of AP may be associated with HO that is spreading extensively over the entire joint, causing severe ankylosis (Orzel *et al.*, 1985; Rossier *et al.*, 1973). The finding of increased serum P during the period of bone resorption is compatible with an increase in the number of osteoblasts.

The data we have collected suggest that the relationship between AP, P, or Ca values alone and HO is not statistically significant (Table I), and that elevation of AP and P together, based on one blood test, occurred more often in patients with HO than in those without HO (Table II), but the difference was not statistically significant. Until now the diagnostic significance of elevated levels of both AP and P in HO has been studied.

It might be presumed that fracture or bone surgery (e.g. spinal fusion) may be associated with elevated blood levels of AP and P, but our findings failed to provide evidence of a relationship between fracture and HO. This seems to suggest that AP and P are more related to the development of HO than fracture or bone surgery.

The literature describes different time periods ranging from 19 days to 4 months for the development of HO following SCI (Silver, 1969; Venier *et al.*, 1971; Stover, 1986). The development of HO in our sample was distributed across phases as follows: phase 1, 4 patients (22%); phase 2, 7 patients (39%); phase 3, 6 patients

(33%); and phase 4, 1 patient (6%). The difference in percentages was not statistically significant.

Our findings show no significant relationship between HO and the completeness of injury. We found a non-significant difference between the percentage of patients with HO in the cervical (10·3%) and thoracic (23·1%) groups. However, significant differences were found between the cervical and lumbar (0·0%) and the thoracic and lumbar groups. Our results, therefore, differ from those of Damanski (1961), who reported that the peak incidence of HO was at thoracic spinal levels, and from those of Knudsen *et al.* (1982), who found that those with HO were more likely to have complete lesions.

The present study does not totally clarify the role of AP as a diagnostic tool for determining the presence of HO. AP did increase in 44·4% of our patients with HO, but it was also elevated in 63·9% of those without HO. Figure 1, however, shows that a higher percentage of blood tests revealing elevated AP levels is associated with a greater likelihood that HO has developed. Approximately 50% of patients with HO showed elevated AP levels 50% or more of the time, whereas this was true in only about 20% of non-HO patients.

Our results confirm the results of Rossier *et al.* (1973), that is, that serum P determinations, when evaluated alone, are of little value in the diagnosis of HO. Table I and Figure 3 show, and the statistical analysis confirms, that there are no differences between the HO and non-HO groups in the percentage of patients with elevated P.

Our study reveals, however, that serum P can be of diagnostic value when evaluated with AP. Table II shows that 61·1% of our HO sample had elevations of both AP and P and 43·4% of the non-HO group had elevations of both values. This difference was statistically non-significant and, in practical terms, is not very large, and may therefore be of limited diagnostic value. Figure 3, however, further amplifies the value of increased AP and P in the diagnosis of HO. This Figure shows that as the proportion of blood tests showing both elevated AP and P levels rises, the likelihood that the patient has HO increases. Only about 5% of the non-HO patients showed elevations of both AP and P on 50% or more of their blood tests, while this was true in approximately 30% of those with HO. Although having normal serum levels of both AP and P does not rule out the presence of HO, persistent elevation of both values greatly increases the likelihood that the patient has HO.

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